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The effect of crown-ether on the palladium-catalyzed Ullmann-type coupling mediated by zinc in air and water

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Abstract

In the presence of a catalytic amount of 18-crown-6, palladium-catalyzed reductive coupling of aryl halides mediated by zinc was found effective in water alone, at ambient temperature, and under an atmosphere of air to give improved isolated yield of the Ullmann-type reaction products.

The Ullmann reaction is one of the fundamental reactions in organic chemistry. The reaction has been widely used in synthesizing various aromatic compounds. Under the classical conditions, the reaction[1,2] is mediated by copper.[3] Generally, the Ullmann coupling is also carried out at a high temperature. Recently, it has been shown that these reactions can be carried out under mild conditions, in the presence of copper(I) thiophene-2-carboxylate.[4] Palladium-catalyzed reductive couplings are among the most important carbon–carbon bond forming reactions in modern synthetic organic chemistry.[5] These reactions are generally air sensitive. It was known that palladium can catalyze aryl halide homo-couplings under elevated reaction temperatures in the presence of a reducing reagent.[6]

Recently, we reported a palladium-catalyzed Ullmann-type reductive coupling of aryl halides in aqueous conditions[7] and under an air atmosphere.[8] During the reaction, compounds formed due to the reductive dehalogenation of the halides are potential by-products (which are volatile). In order to determine the ratio of the desired product and by-product formed during the reaction, we capped the reaction vessel and, after the reaction, extracted the reaction mixture fully with an organic solvent. Then the mixture was directly subjected to GC–MS analysis, which provided the conversion of the starting materials and the ratios of product/by-product. On careful examining the reaction further, we noticed relatively low isolated yield of the desired product for coupling of iodobenzene, which falls in the range of 20–30% after column chromatography on silica gel

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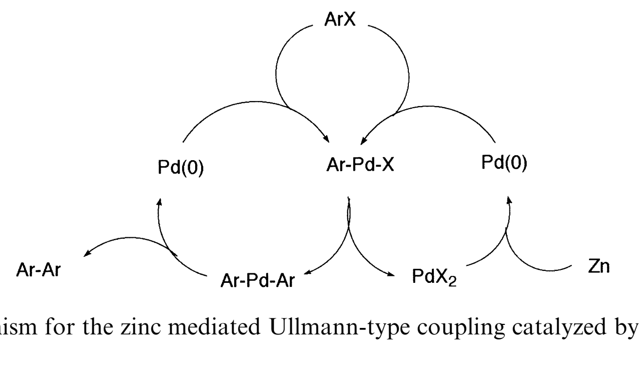
(while no other product can be isolated). Initially, we attributed the low mass-balance to isolation loss during the column chromatography. Our further investigations of the reaction under improved conditions provided much higher isolated yields of the product, which inferred that although the reaction has a high conversion, under the conditions reported earlier, a fair amount of the volatile dehalogenation product was probably formed and was lost during the reaction. Here we present that, in the presence of a catalytic amount of 18-crown-6, the zinc mediated reductive coupling of aryl halides catalyzed by Pd/C provided improved isolated yields of the products at ambient temperature, in water alone, and under an atmosphere of air (Eq. (1)).[9]

$$\mathrm{ArX} \xrightarrow[\text{Zn, } \mathrm{H_2O}\text{/18-crown-6, air, ambient temperature}]{\text{Pd/C cat.}} \mathrm{Ar\text{-}Ar} \qquad (1)$$

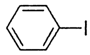
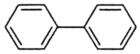
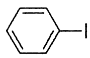
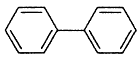
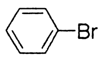
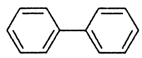
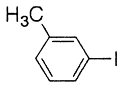
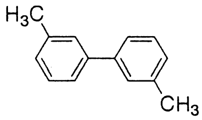
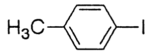
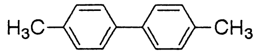
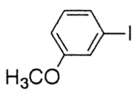
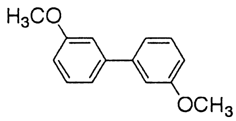
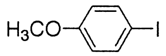
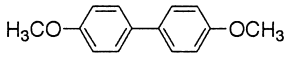
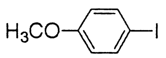
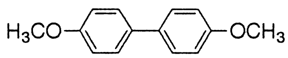
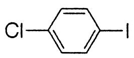
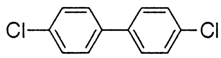
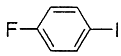
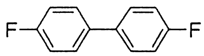
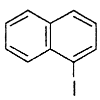
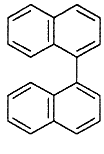
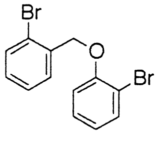
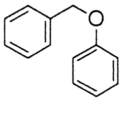
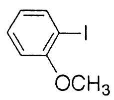
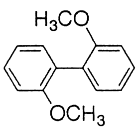
As shown in Table 1, various aromatic iodides and bromides were coupled by zinc in water with the presence of catalytic amounts of Pd/C and 18-crown-6. In the absence of the crown ether, the yield of the desired product diminished considerably (compare entries 1 and 2, 7 and 8). The improvement of product yield in the presence of crown ether could be due to either a stabilization of the arylpalladium intermediate or a surfactant effect, which is under further investigation. Aryl chloride and fluoride were inert under the reaction conditions. An increase in steric hindrance resulted in a decrease of the yield of the coupled product (compare entries 6, 7, and 13).

Regarding the mechanism of the reaction, subsequent to our report Sasson and co-workers described a palladium-catalyzed reductive coupling of aryl halides under a hydrogen gas atmosphere.[10] Very recently, the researchers proposed that the reaction in our earlier report proceeded via a mechanism involving the reduction of palladium intermediate by hydrogen gas generated by the reaction of zinc with water.[11] While we do not exclude such a possibility of hydrogen gas participation, we believe that the reaction in our case most likely proceeded via a direct electron transfer from zinc to palladium(II) (or via the reaction medium) which completed the catalytic cycle (Scheme 1). As likely experimental evidence to support such a direct metal-to-metal electron transfer, entry 12 provided a 70% isolated yield of dehalogenation product while maintaining the benzylic functionality, which is known to undergo hydrogenolysis efficiently.[12] In conclusion, the use of a catalytic amount of a crown ether allows us to obtain good isolated yields of the zinc-mediated, palladium-catalyzed Ullmann-type reductive coupling in water and under an air atmosphere.



Scheme 1. Proposed mechanism for the zinc mediated Ullmann-type coupling catalyzed by palladium in air and water

Table 1
Zinc mediated reductive coupling of aryl halides catalyzed by Pd/C under air atmosphere

entry	substrate (**1**)	product (**2**)	isolated yield (%)
1			54
2			21[c]
3			44
4			61
5			68
6			57
7			51
8			12[c]
9			60
10			60
11			~40[a]
12			70[b]
13			40

Yields were isolated ones after a short chromatography on silica gel. a). The product was isolated as a mixture of coupling and dehalogenation, with the ratio being estimated by GC/MS; b). No coupling product was isolated; c). No crown-ether was added.

Acknowledgements

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9. All products are known compounds and were characterized by NMR and GC–MS. Experimental procedure: To a suspension of 4-iodotoluene (300 mg, 1.3 mmol) in 10 mL of de-ionized water in a 50 mL test-tube was added Pd/C (10%, 291 mg, 0.27 mmol), 18-crown-6 (73 mg, 0.27 mmol) and zinc powder (273 mg, 4.12 mmol). The mixture was capped and stirred overnight, diluted with 4 mL 1N aqueous HCl, filtered through Celite and washed with ether. The filtrate was extracted with ether and concentrated. The resulting crude material was passed through a short column of silica gel to give 4,4′-dimethylbiphenyl (85 mg, 68%).
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